42. A low salt-containing aqueous composition comprising biologically active recombinant human IGF-I is a concentration of about 350 mg/ml, and wherein said composition has a density of about 1.07 g/ml and a viscosity of about 15,700 cps and a pH greater than about pH 5.0.

43. A pharmaceutical composition comprising the composition of claim 42, and a pharmaceutically acceptable carrier and/or excipient.

REMARKS

Introductory Comments

Claims 1, 3-7, 9-11, and 13-44 were pending. Claims 5-7, 9-11, 14, 15, and 21-27 were withdrawn as being drawn to a nonelected invention. The Examiner has rejected claims 1, 3, 4, 13, 16-20, and 28-44.

The Examiner has rejected claims 1, 3, 4, 13, 18-20, and 28-44 under 35 U.S.C. §112, first paragraph, asserting that the specification does not reasonably provide enablement commensurate in scope with the claims.

The Examiner has rejected claim 1 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite as to the structure of the variants being claimed.

The Examiner has rejected claims 1, 13, 34, and 42 under 35 U.S.C. §112, second paragraph, asserting that the claims are made indefinite by citing the terminologies "low, less than, greater than, at least."

The Examiner has rejected claims 1, 3, 4, 13, 16-20, and 28-42 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite due to the lack of pH of the buffer in the formulation, and by the use of the term "mg/ml."

The Examiner rejected claim 13 as an improper kit claim.

The Examiner rejected claims 16, 38, 40, and 43 as duplicative of claims 1, 34, 40, and 42, respectively.

The Examiner has rejected claims 1, 3, 4, 16-20, 28-38, and 42-44 under 35 U.S.C. §103(a), asserting that the claims are unpatentable over U.S. Patent No. 5,410,026 to Chang *et al.* (1995).

The Examiner has rejected claims 39-41 under 35 U.S.C. §103(a), asserting that the claims are unpatentable over U.S. Patent No. 5,410,026 to Chang *et al.* (1995), in view of Johnson *et al.* (1996).

These rejections are traversed and believed to be overcome for reasons discussed below.

Overview of the Amendments

Claims 1, 34, and 42 have been amended to specify that the compositions are "aqueous" compositions. The amendments to the claims find support on page 3, lines 14-21.

Claims 1, 34, and 42 have additionally been amended to specify that the pH of the compositions is greater than about pH 5.0. The amendments to the claims find support on page 8, lines 3-8.

Claim 1 has been amended to recite that the variant is a polypeptide that has at least 80% amino acid sequence identity to the amino acid sequence of human IGF-I. The amendment finds support in the specification at page 9, lines 17-19.

Claim 13 has been amended to recite that the kit comprises the composition and the buffer separately. Support for the amendment can be found on page 3, lines 1-3.

Claims 16, 38, 40, and 43 have been amended to specify that the pharmaceutical compositions also contain a pharmaceutically acceptable carrier and/or excipient. The amendments to the claims find support on page 15, lines 27-30, and page 16, line 12 to page 17, line 3.

Accordingly, no new matter has been added by way of this amendment and the entry thereof is respectfully requested.

The Invention

Before addressing the Examiners objections and rejections, the applicants reiterate the invention claimed in the compositions of the independent claims. The new composition of matter comprises human IGF-1 or its biologically active variant. The characteristics of these compositions are that they are (a) low salt-containing; (b) are biologically active; and (c) high concentrations of the biologically active polypeptides are

present. Previously known high concentrations of IGF-1 were found in inclusion bodies. However, IGF-1 in such inclusion bodies is generally misfolded and biologically inactive, and must therefore be reduced, refolded and resolubilied into an active, solubilized form. Thus, the Examiner will appreciates, low salt-containing compositions of IGF-1 or its analog that are present at high concentrations and still biologically active without the need for refolding are novel to this invention.

Addressing the Examiner's Rejections

1. Rejection of Claims 1, 3, 4, 13, 18-20, and 28-44 under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1, 3, 4, 13, 18-20, and 28-44 under 35 U.S.C. §112, first paragraph, asserting that the specification does not reasonably provide enablement commensurate in scope with the claims. The Examiner suggested that pH should be included in the claims.

The applicants traverse the rejection since the specification provides detailed instructions for preparing the composition of the invention by either manipulating the pH of the solution, or by using solubility enhancers, and the stability of the claimed composition does not depend on its pH. However, in order to further prosecution of the application, the applicants have amended the independent claims 1, 34, and 42 to recite that the pH of the composition is greater than about 5.0. The Examiner is respectfully requested to withdraw this rejection.

2. Rejection of Claims under 35 U.S.C. §112, Second Paragraph

A) The Examiner has rejected claim 1 and its dependent claims under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner has asserted that the use of the terminology "biologically active variants thereof" renders the claims indefinite as to the structure of the variants being claimed.

Under 35 U.S.C. §112, second paragraph, absolute specificity and precision are not required in the claims. Claims need only reasonably apprise a person having ordinary skill in the art as to their scope. *Hybritech Inc., v. Monoclonal Antibodies, Inc.,* 231 USPQ 81, Fed. Cir. 1986. A claim which is clear to one ordinarily skilled in the art when read in light of the Specification, does not fail for indefiniteness. *Allan Archery, Inc. v. Browning Manufacturing Co.*, 819 F.2d 1087, 2 USPQ2d 1490 (Fed. Cir. 1987).

Claim 1 recited that the "variant is a polypeptide that has IGF-I activity and differs from the amino acid sequence for said human IGF-I by up to 10 amino acid residues." Thus, the variants are claimed with reference to structure. Accordingly, claim 1, and those claims dependent thereon are considered sufficiently definite.

Applicants have defined the boundaries of the term "variant" within the claims by defining it in terms of its activity and in terms of its sequence identity to the native IGF-I. The specification describes variants having IGF-I activity and provides detailed assays for determining IGF-I activity at page 8, line 24 to page 9, line 2, and page 9, lines 17-21. The specification notes that the variants can differ by up to 10, 5, 4, 3, 2, or 1 amino acid residues, but has at least the same activity as the native molecule. Accordingly, the applicants submit that the use of the "biologically active variants thereof" terminology is not indefinite.

In view of the teachings of the specification and the level of ordinary skill in the present art, the applicant submits that the boundaries of claim 1 are capable of being understood by one of ordinary skill in the art. Accordingly, applicant submits that the rejections of the claims under 35 U.S.C. §112, second paragraph, should be withdrawn. However, the applicants have amended the claim to define the variant as having at least 80% amino acid sequence identity to the amino acid sequence of human IGF-1, thereby making the rejection moot.

With respect to claim 21, applicants note the Examiner's suggestion to incorporate the recitation from claim 28 therein. Applicants point out claim 21 was withdrawn from examination since it was drawn to a nonelected invention. Therefore, the Examiner's suggestion was not followed, and request the Examiner provide an explanation if the rejection is maintained.

B) The Examiner has rejected claims 1, 13, 34, and 42 under 35 U.S.C. §112, second paragraph, asserting that the claims are made indefinite by citing the terminologies "low, less than, greater than, at least."

The applicants traverse the rejection. The second paragraph of 35 U.S.C. §112 merely requires that an applicant set out and circumscribe a particular subject area with a reasonable degree of precision such that the metes and bounds of the invention are set forth. *Ex parte Head*, 214 USPQ 551, PTO Bd. App. 1981. In the MPEP, §2173.05(b) discusses the use of the relative terminology in the claims. According this section of the MPEP, the use of the relative terms does not automatically render the claim indefinite. Instead, "[a]cceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." Thus, the Examiner's broad assertion that the use of relative terminology makes the claims indefinite is incorrect. The use of the relative terminology in the claims is acceptable practice as discussed in the case law and in the MPEP, and their use should be determined on a case by case basis.

The "low salt-containing" compositions of claims 1, 34, and 42 are defined on page 4, lines 11-13, as composition with an amount of salt that is insufficient to cause precipitation of the protein. Applicants further provide experimental details in Example 5 on page 23 for preparing salt-containing compositions and a test for distinguishing the "low salt-containing" compositions of the present invention from salt-containing compositions. Further, the use of the term should be determined in the context in which the term is utilized. In the context of the rejected claims, the term defines aqueous compositions are that they are (a) low salt-containing; (b) are biologically active; and (c) high concentrations of the biologically active polypeptides are present. Based on the description provided in the specification and the context in which it is used in the claims, the applicants submit that the phrase "low salt-containing" would be understood by one of skill in the art, and the term is definite. The Examiner is respectfully requested to withdraw this rejection.

The Examiner rejected the claims as indefinite for citing the terminologies "low, less than, greater than, at least." In the present invention, the context in which the objected to terms are employed in the claims are "at least about 250 mg/ml," "pH less

than or equal to pH 5.0," and "a pH greater than." In this context, the use of the terms is conventional thereby conveying to one of ordinary skill in the art the metes and bounds of the present claim language. The Examiner has not indicated how or why the language to which the Examiner has objected would lead to uncertainty in interpreting of the metes and bounds of the present claims when read in their entirety. Therefore, the Examiner is respectfully requested to withdraw the rejection.

C) The Examiner has rejected claims 1, 3, 4, 13, 16-20, and 28-42 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite due to the lack of pH of the buffer in the formulation, and by the use of the term "mg/ml."

As suggested by the Examiner, claims 1, 34, and 42 have been amended to recite "aqueous" compositions, and the independent claims now recite that the pH of the composition is greater than about 5.0. The Examiner is respectfully requested to withdraw the rejection.

D) The Examiner rejected claim 13 as an improper kit claim. The claim has been amended to make clear that the kit comprises the composition of claim 1 and, separately, a pharmaceutically acceptable buffered solution. Thus, this rejection is obviated by way of amendment to the claims.

E) The Examiner rejected claims 16, 38, 40, and 43 as duplicative of claims 1, 34, 40, and 42, respectively. The rejected claims have been amended to recite that the pharmaceutical compositions additionally comprise a pharmaceutically acceptable carrier and/or an excipient. Thus, this rejection is obviated by way of amendment to the claims.

3. The Rejection of Claims Under 35 U.S.C. §103(a)

A) The Examiner has rejected claims 1, 3, 4, 16-20, 28-38, and 42-44 under 35 U.S.C. §103(a), asserting that the claims are unpatentable over U.S. Patent No. 5,410,026 to Chang *et al.* (1995). The Examiner stated that Chang *et al.* teaches the use of chaotropic agents in a single buffer to increase the solubility of an IGF-I in solution.

Applicants traverse the rejection. The present invention is directed towards low salt-containing aqueous compositions at a concentration of at least about 250 mg/ml. As discussed above, the characteristics of the inventive compositions are that they are (a) low salt-containing; (b) contain biologically active protein; and (c) high concentrations of the biologically active polypeptides are present.

In contrast, Chang *et al.* is concerned with the biologically inactive and improperly folded form of IGF-1 found in inclusion bodies. In addition, the cited reference pertains to dilute solutions. As discussed above and in the specification, IGF-1 in such inclusion bodies is generally misfolded and biologically inactive, and must therefore be reduced, refolded and resolubilied into an active, solubilized form. Chang *et al.* provide a method for refolding an insoluble and improperly folded IGF-I precipitate. The authors state in the abstract that the IGF-I is solubilized "at concentrations sufficiently low to allow solubilization" to occur. Further, at column 10, line 68 to column 11, line 3, the authors state that the concentration of IGF-I is preferably in the 1.5-5.0 mg/ml. Thus, the cited reference discloses a solution having a much lower concentration of IGF-I. The applicants' invention pertains to aqueous compositions that are (a) low salt-containing; (b) are biologically active; and (c) high concentrations of the biologically active polypeptides are present, while the cited reference pertains to either misfolded, biologically inactive IGF present in high concentrations, or biologically active IGF that is present in very low concentrations. They do not teach or suggest that a biologically active, highly concentrated solution of IGF-I can be prepared by their method. Thus, the cited reference does not teach or suggest all of the claim limitations. In fact, by teaching that the concentration of IGF-I should be low, the cited reference teaches away from the compositions of the invention that comprise biologically active human IGF-I or biologically active variant thereof in a concentration of at least about 250 mg/ml.

In the absence of some teaching or suggestion in the cited reference concerning the composition of the present invention, the Examiner has presented no more than an improper hindsight reconstruction of the present invention. Accordingly, the applicants respectfully requests withdrawal of the rejections under 35 U.S.C. §103.

B) The Examiner has rejected claims 39-41 under 35 U.S.C. §103(a), asserting that the claims are unpatentable over U.S. Patent No. 5,410,026 to Chang *et al.* (1995), in view of Johnson *et al.* (1996). The Examiner stated that Chang *et al.* do not teach the incorporation of their product in PLGA microspheres, but such encapsulation is taught by Johnson *et al.*

Applicants traverse the rejection. The rejected claims are dependent claims, and, therefore, contain all the limitations of the independent claim from which they depend. Since the independent claims are patentable over the cited art, the dependent claims are also patentable.

As discussed in detail above, Chang *et al.* do not teach or suggest the compositions of the invention. In fact, they teach away from the present invention by suggesting that the concentration of IGF-I should be low, most preferably in the range of 1.5-5.0 mg/ml. Essentially, Chang *et al.* teach a improperly folded and biologically inactive IGF-1 in high concentrations or a biologically active IGF-1 at low concentrations. The deficiencies in Chang *et al.* are not cured by Johnson *et al.* Therefore, the combination of the references can not teach the composition of the invention. Even if the combination were to teach the compositions of the invention, they do not teach or suggest encapsulating the compositions comprising biologically active human IGF-1 or a biologically active variant thereof in PLGA and microspheres. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Filing Date

As previously noted in the Petitions dated January 5, 1999 and June 5, 2000, this application was granted the improper filing date of November 5, 1998, through no error on part of the applicants. Applicants respectfully request the granting of November 6, 1998 as the filing date for the present invention.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Please direct all further written communications regarding this application to:

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Respectfully submitted,

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Appendix A

Marked-up Version

1. A low salt-containing aqueous composition comprising biologically active human IGF-I or biologically active variant thereof in a concentration of at least about 250 mg/ml and a pH greater than about pH 5.0, wherein said variant is a polypeptide that has at least 80% amino acid sequence identity to amino acid sequence of the human IGF-I [activity and differs from the amino acid sequence for said human IGF-I by up to 10 amino acid residues].

13. A kit for reconstituting a pharmaceutical composition comprising biologically active human IGF-I or biologically active variant thereof, said kit comprising the composition of claim 1 and separately a pharmaceutically acceptable buffered solution having a pH less than or equal to pH 5.0.

16. A pharmaceutical composition comprising the composition of claim 1, and a pharmaceutically acceptable carrier and/or excipient.

34. A low salt-containing aqueous composition comprising biologically active human IGF-I in a concentration of at least about 250 mg/ml and a pH greater than about pH 5.0.

38. A pharmaceutical composition comprising the composition of claim 34, and a pharmaceutically acceptable carrier and/or excipient.

40. A pharmaceutical composition comprising the composition of claim 37, and a pharmaceutically acceptable carrier and/or excipient.

42. A low salt-containing aqueous composition comprising biologically active recombinant human IGF-I is a concentration of about 350 mg/ml, and wherein said composition has a density of about 1.07 g/ml and a viscosity of about 15,700 cps and a pH greater than about pH 5.0.

43. A pharmaceutical composition comprising the composition of claim 42, and a pharmaceutically acceptable carrier and/or excipient.

Appendix B

Claims Pending

1. A low salt-containing aqueous composition comprising biologically active human IGF-I or biologically active variant thereof in a concentration of at least about 250 mg/ml and a pH greater than about pH 5.0, wherein said variant is a polypeptide that has at least 80% amino acid sequence identity to the amino acid sequence of human IGF-I.

3. The composition of claim 1, wherein said human IGF-I or variant thereof is present in a concentration of about 250 mg/ml to about 500 mg/ml.

4. The composition of claim 1, wherein said human IGF-I or variant thereof is present in a concentration of about 350 mg/ml, and wherein said composition has a density of about 1.07 g/ml and a viscosity of about 15,700 cps.

13. A kit for reconstituting a pharmaceutical composition comprising biologically active human IGF-I or biologically active variant thereof, said kit comprising the composition of claim 1 and separately a pharmaceutically acceptable buffered solution having a pH less than or equal to pH 5.0.

16. A pharmaceutical composition comprising the composition of claim 1, and a pharmaceutically acceptable carrier and/or excipient.

17. The pharmaceutical composition of claim 16, wherein said composition is a sustained-release formulation.

18. The pharmaceutical composition of claim 16, wherein said composition is a gel formulation

19. A cryogenically produced PLGA microsphere comprising the composition of claim 1.

20. The microsphere of claim 19, wherein said microsphere comprises a lyophylized form of said composition.

28. The composition of claim 1, wherein said variant differs from the amino acid sequence for said humang IGF-I by up to 5 amino acid residues.

29. The composition of claim 1, wherein said variant differs from the amino acid sequence for said human IGF-I by up to 2 amino acid residues.

30. The composition of claim 1, wherein said variant differs from the amino acid sequence for said human IGF-I by 1amino acid residue.

31. The composition of claim 1, wherein said human IGF-I is recombinant human IGF-I.

32. The composition of claim 1, wherein said recombinant human IGF-I is present at a concentration of about 250 mg/ml to about 500 mg/ml.

33. The composition of claim 1, wherein said recombinant human IGF-I is present at a concentration of about 350 mg/ml, and wherein said composition has a density of about 1.07 g/ml and a viscosity of about 15,700 cps.

34. A low salt-containing aqueous composition comprising biologically active human IGF-I in a concentration of at least about 250 mg/ml and a pH greater than about pH 5.0.

35. The composition of claim 34, wherein said human IGF-I is recombinant human IGF-I.

36. The composition of claim 34, wherein said human IGF-I is present at a concentration of about 250 mg/ml to about 500 mg/ml.

37. The composition of claim 34, wherein said human IGF-I is present at a concentration of about 350 mg/ml, and wherein said composition has a density of about 1.07 g/ml and a viscosity of about 15,700 cps.

38. A pharmaceutical composition comprising the composition of claim 34, and a pharmaceutically acceptable carrier and/or excipient.

39. A cryogenically produced PLGA microsphere comprising the composition of claim 34.

40. A pharmaceutical composition comprising the composition of claim 37, and a pharmaceutically acceptable carrier and/or excipient.

41. A cryogenically produced PLGA microsphere comprising the composition of claim 37.

42. A low salt-containing aqueous composition comprising biologically active recombinant human IGF-I is a concentration of about 350 mg/ml, and wherein

said composition has a density of about 1.07 g/ml and a viscosity of about 15,700 cps and a pH greater than about pH 5.0.

43. A pharmaceutical composition comprising the composition of claim 42, and a pharmaceutically acceptable carrier and/or excipient.

44. A cryogenically produced PLGA microsphere comprising the composition of claim 42.